

#1075

THE COUNCIL FOR TOBACCO RESEARCH—U.S.A., INC.

110 EAST 58TH STREET
NEW YORK, N. Y. 10022
(212) 421-8383

Application for Research Grant
(Use extra pages as needed)

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Date: 1/30/75

1. Principal Investigator (give title and degrees):

A. Charles Mittman, M.D., Director, Respiratory Disease Department
B. Jack Lieberman, M.D., Associate Director, Respiratory Disease Dept.

2. Institution & address:

City of Hope Medical Center
1500 East Duarte Road
Duarte CA 91010

3. Department(s) where research will be done or collaboration provided:

Respiratory Disease Department, City of Hope Medical Center,
Duarte, California 91010

4. Short title of study:

Round Heart Disease in Turkeys: A model of Antitrypsin Deficiency
in Man

5. Proposed starting date: July 1, 1975

6. Estimated time to complete: Three years

7. Brief description of specific research aims:

Investigators at the Kimron Veterinary Institute of Tel Aviv University, Israel, have demonstrated that the pathology in turkey round heart disease (RHD) shares certain features with antitrypsin deficiency in man (see accompanying application). Specifically, birds who die with RHD have a deficiency of alpha₁-globulins and specific intracytoplasmic globules in their liver cells. Studies on material sent to our laboratory from Israel confirm that the histochemical properties of the globules and their location in rough endoplasmic reticulum are identical to that seen in human material. We are currently conducting studies on material from turkeys dying of RHD in California.

This proposal requests funds to permit continued collaboration between our laboratory and the investigators in Israel. Specifically, we will be responsible for the following aspects of the study:

- 1) Consult with the Israeli investigators and assist in establishing procedures for the electrophoretic differentiation of the normal and aberrant alpha₁ protease inhibitor.
- 2) Chemically characterize the inhibitor isolated from the liver of normal and deficient turkeys.
- 3) Carry out electron microscopic studies of tissues from diseased and normal turkeys.
- 4) Determine if the condition recognized as round heart disease in turkeys in the United States is the same as that observed in Israel.

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8. Brief statement of working hypothesis:

2.

See application of Trainin, et al)

9. Details of experimental design and procedures (append extra pages as necessary)

For a number of years our laboratory has been studying various aspects of α_1 -antitrypsin deficiency (AATD) in man. Progress in understanding the basic defect in this inherited condition would be greatly accelerated if an animal model of the deficiency were available. Turkey round heart disease (RHD) appears to be associated with the same hepatic abnormality seen in human antitrypsin deficiency. Accordingly, study of RHD may yield important insights as to the cellular defect which interferes with normal hepatic synthesis and/or release of antitrypsin. The group at the Kimron Veterinary Institute in Israel first recognized the similarity between RHD and AATD. They are ideally situated to carry out certain aspects of the proposed research. Specifically, they have ready access to large numbers of diseased and healthy birds, have the facilities needed to carry out the crucial breeding studies, and are in possession of most of the equipment and skills needed for this project. Our group will contribute its experience with the various-electrophoretic techniques for identifying variant antitrypsin types and its familiarity with the methods for isolating and characterizing the protein in liver and serum. (Please see reprint, Matsubara, Yoshida and Lieberman. Proc Nat Acad Sci 71:3334, 1974.) The necessary electron microscopic studies of various tissues will be performed in our laboratory. (Please see reprint, Gordon, Dixon, Rogers, Mittman, and Lieberman. Human Path 3:361, 1972.) Finally, techniques similar to those outlined above will be applied to material from turkeys dying of RHD in the United States.

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10. Space and facilities available (when elsewhere than item 2 indicates, state location):

The Biochemistry Laboratory of the Respiratory Disease Department, City of Hope Medical Center, occupies 1600 square feet and contains all the equipment needed to carry out the required electrophoretic and biochemical studies. Protein characterizations are conducted in collaboration with the Department of Biochemical Genetics at the City of Hope (Dr. A. Yoshida, Director). Electron microscopy is performed using the facilities of the Department of Pathology, Laboratory of Cytogenetics and Electron Microscopy (Dr. R. Teplitz, Director).

11. Additional facilities required:

None

12. Biographical sketches of investigator(s) and other professional personnel (append):

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

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12. Biographical sketch

CURRICULUM VITAE - CHARLES MITTMAN, M.D.

Born:

REDACTED

REDACTED

REDACTED

REDACTED

University of Chicago

A.B. with Honors

B.S. with Honors

M.D. with Honors

REDACTED

McCoy College of Johns Hopkins University

Elective courses in Mathematics

September 1962 to June 1964

University of Chicago

Committee on Mathematical Biology

July 1965 to June 1966

Training and Experience:

Rotating Internship, University of Chicago Clinics
July 1960 to June 1961Junior Assistant Resident in Medicine,
University of Chicago Clinics
July 1961 to December 1961Surgeon, USPHS, Gerontology Branch, National
Heart Institute, Baltimore City Hospital
December 1961 to June 1964Assistant Visiting Physician in Medicine,
Baltimore City Hospital
February 1962 to June 1964Assistant in Medicine, Johns Hopkins University
School of Medicine
July 1963 to June 1964Assistant Resident in Medicine,
University of Chicago Clinics
July 1964 to June 1965USPHS Post-doctoral Fellow, Department of Medicine,
University of Chicago
July 1965 to June 1966Instructor, Department of Medicine,
University of Chicago
January 1966 to December 1966

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Director, Respiratory Disease Department,
City of Hope Medical Center, Duarte, CA
January 1967 to present

Assistant Clinical Professor of Medicine,
UCLA School of Medicine, Los Angeles, CA
June 1967 to June 1973

Associate Clinical Professor of Medicine,
UCLA School of Medicine, Los Angeles, CA
July 1973 to present

PUBLICATIONS

1. Mittman C: Summary of symposium on pulmonary emphysema and proteolysis. Amer Rev Resp Dis 105:430-448, 1972.
2. Mittman C, Barbela TV and Lieberman J: Antitrypsin deficiency and abnormal protease inhibitor phenotypes. Arch Envir Health 27: 201-206, 1973.
3. Mittman C and Lieberman J: Screening for Alpha₁-Antitrypsin deficiency. Israel J Med Sci 9:1311-1318, 1973.
4. Mittman C, Lieberman J and Rumsfeld J: Prevalence of abnormal protease inhibitor phenotypes in patients with chronic obstructive lung disease. Amer Rev Resp Dis 109:295-296, 1974.
5. Mittman C, Pedersen E, Barbela T and Lewis H: Prediction and potential prevention of industrial bronchitis. Amer J Med 57: 192-199, 1974.

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12. Biographical sketch

CURRICULUM VITAE - JACK LIEBERMAN, M.D.

Born:

REDACTED

Marital Status:

REDACTED

Education: University of California at Los Angeles REDACTED
B.A. with honors (Zoology)

Northwestern University - REDACTED
University of Southern California, Los Angeles
M.D. R

Training and Experience:

Internship, Los Angeles County Harbor General
Hospital, 1954-55.

Resident in Internal Medicine, Harbor General
Hospital, 1955-58.

Clinical Assistant in Medicine, UCLA School of
Medicine, 1957-58.

Research Fellow of the Long Beach Heart Association,
Harbor General Hospital, 1958-60.

Clinical Instructor in Medicine, UCLA School of
Medicine, 1958-62.

Attending Staff, Harbor General Hospital, 1960 to present

Clinical Investigator, Veterans Administration Hospital,
Long Beach, 1960-63.

Assistant Clinical Professor in Medicine, UCLA School
of Medicine, 1962-68.

Section Chief, Internal Medicine, Veterans Administra-
tion Hospital, Long Beach, CA. 1963-68.

Associate Clinical Professor in Medicine, UCLA School
of Medicine, 1968-71.

Associate Director, Department of Respiratory Diseases,
City of Hope Medical Center, Duarte, CA. 1968-

Director, Pulmonary Biochemistry Laboratory, City of
Hope Medical Center, 1968-

Associate Clinical Professor in Medicine, University
of California at Irvine School of Medicine, 1971-

Boards:

Diplomate of American Board of Internal Medicine, 1962.

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PUBLICATIONS

1. Lieberman J and Mittman C: Dynamic response of α_1 -antitrypsin variants to diethylstilbestrol. Amer J Human Genet 25:610-617, 1973.
2. Lieberman J: Plasma arginine esterase activity in cystic fibrosis. Amer Rev Resp Dis 109:399-400, 1974.
3. Lieberman J: Editorial: Emphysema, cirrhosis, and hepatoma with α_1 -antitrypsin deficiency. Ann Int Med 81:850-852, 1974.
4. Lieberman J: Carboxypeptidase B-like activity and C3 in cystic fibrosis. Amer Rev Resp Dis 111:100-102, 1975.
5. Matsubara S, Yoshida A and Lieberman J: Material isolated from normal and variant human liver that immunologically crossreacts with α_1 -antitrypsin. Proc Nat Acad Sci 71:3334-3337, 1974.

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14. First year budget:

A. Salaries (give names or state "to be recruited")

Professional (give % time of investigator(s)
even if no salary requested)

% time

Amount

Charles Mittman, MD

10

-

Jack Lieberman, MD

10

-

Technician

25

2,500

Technical

Sub-Total for A

2,500

B. Consumable supplies (by major categories)

Animals

50

Reagents, antibody, etc.

100

Sub-Total for B

150

C. Other expenses (itemize)

Electron microscopy on approximately
10 sets of tissues

2000

Airfreight and shipping of samples

500

Travel to Israel

1200

Travel within the U.S.

500

Sub-Total for C

4,200

Running Total of A + B + C

7,850

D. Permanent equipment (itemize)

None

Sub-Total for D

E

1,027

E. Indirect costs (15% of A+B+C)

Total request

7,877

15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	3,000	150	4,500	0	1,147	8,797
Year 3	3,500	200	4,500	0	1,230	9,130

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16. Other sources of financial support:

List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Dr. Mittman: Genetic and Environmental Influences on Lung Disease	Public Health Serv. HL12833	32,349	9/1/74 to 8/31/75
Dr. Lieberman: Alpha-1-Antitrypsin Deficiency in Pulmonary Emphysema	Public Health Service HL13398	41,516	1/1/75 to 12/31/75

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Dr. Mittman: Genetic and Environmental Influences on Lung Diseases	Renewal of Public Health Service HL12833	170,836	9/1/75 to 8/31/78

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Charles Mittman

Signature Charles Mittman Date 1-20-76

Telephone 213 3598111 771
Area Code Number Extension

Checks payable to

City of Hope Medical Center

Mailing address for checks

1500 East Duarte Road

Duarte CA 91010

Responsible officer of institution

Typed Name Elihu King

Title Assistant Administrator

Signature Elihu King Date 1-20-76

Telephone 213 359-8111 709
Area Code Number Extension

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